FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL CONVENTIONAL TABLET

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

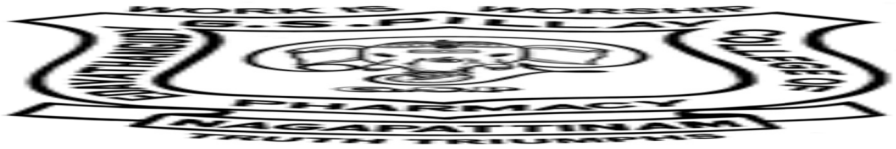
MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

Reg No:261211160



DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

APRIL 2014

FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL CONVENTIONAL TABLET

A dissertation submitted to

THE TAMILNADU Dr.M.G.R MEDICAL UNIVERSITY

CHENNAI- 600 032.

In partial fulfillment of the requirements for the award of Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted
By

RAMRAJ R

(Reg No:261211160)

Under the guidance of

Prof.K.Shahul Hameed Maraicar,M.Pharm,Ph.D.,

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

APRIL 2014

Prof.K.Shahul Hameed Maraicar,M.Pharm,Ph.D.,

Director cum Professor,

Department of Pharmaceutics,

Edayathangudy.G.S.Pillay College of Pharmacy,

Nagapattinam – 611 002.

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL CONVENTIONAL TABLET"** submitted by **RAMRAJ R** (Reg No:261211160) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S.Pillay College of Pharmacy during the academic year 2013-2014.

Place: Nagapattinam

Date:

Prof.K.Shahul Hameed Maraicar,M.Pharm,Ph.D.,

Prof.Dr.D.Babu Ananth,M.Pharm., Ph.D.,

Principal,

Edayathangudy.G.S.Pillay College of Pharmacy,

Nagapattinam – 611 002.

CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL CONVENTIONAL TABLET"** submitted by **RAMRAJ R** (Reg No:261211160) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under the guidance of **Prof.K.Shahul Hameed Maraicar,M.Pharm,Ph.D.,** Director cum Professor, Department of Pharmaceutics, Edayathangudy.G.SPillay College of Pharmacy during the academic year 2013-2014.

Place: Nagapattinam **Prof.Dr.D.BabuAnanth,M.Pharm., Ph.D.,**

Date:

ACKNOWLEDGEMENT

I would like to express profound gratitude to **Chevalier Thiru.G.S.Pillay,** Chairman, E.G.S.Pillay College of Pharmacy, and **Thiru. S.Paramesvaran, M.Com., FCCA.,** Secretary, E.G.S.Pillay College of Pharmacy.

I express my sincere and deep sense of gratitude to my guide **Prof.K.Shahul Hameed Maraicar,M.Pharm,Ph.D.,** Director cum Professor, Department of Pharmaceutics, E.G.S.Pillay College of Pharmacy, for his invaluable and extreme support, encouragement, and co-operation throughout the course of my work.

It is my privilege to express my heartfelt thanks to **Prof.Dr.D.Babu Ananth, M.Pharm, Ph.D.,** Principal, E.G.S.Pillay College of Pharmacy, for providing me all facilities and encouragement throughout the research work.

I wish to express my great thanks to **Prof.Dr.M.Murugan, M.Pharm.,Ph.D.,** Director cum Professor , Department of Pharmaceutics, E.G.S.Pillay College of Pharmacy, for his support and valuable guidance during my project work.

I would like to extend my thanks to all the **Teaching Staff** and **Non Teaching Staff**, who are all, supported me for the successful completion of my project work.

Last but not least, I express my deep sense of gratitude to my parents, family members and friends for their constant valuable blessings and kindness.

INDEX

INTRODUCTION

1.1. Hypertension Epidemiology:

Cardiovascular diseases such as coronary heart disease and stroke are the largest causes of death in developing countries and are one of the main contributors to disease burden. Between years 1990 and 2020 these diseases are anticipated to increase by 120% for women and 137% for men in developing countries. In India about 70% of coronary heart disease-related deaths occur in people younger than 70 years compared with 22% in the west and 94% stroke deaths occurs in people less than 70 years in contrast to 6% in developed countries. Blood pressure (BP) is directly associated with risks of several types of cardiovascular diseases and the associations of BP with disease risk are continuous with large proportions of most populations having non-optimal blood pressure values. In India cardiovascular diseases cause 1.5 million deaths annually. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths. This fact is important because hypertension is a controllable disease and a 2 mm Hg population wide decrease in BP can prevent 151,000 stroke and 153,000 coronary heart disease deaths. Better control can lead to prevention of 300,000 of the 1.5 million annual deaths from cardiovascular diseases in India.

1.2. Etiology of Hypertension:

Blood pressure is the force with which blood pushes against the artery walls as it travels through the body. Blood pressure is measured by two numbers—systolic pressure and diastolic pressure. Systolic pressure measures cardiac output and refers to the pressure in the arterial system at its highest. Diastolic pressure measures peripheral resistance and refers to arterial pressure at its lowest. Blood pressure is normally measured at the brachial artery with a sphygmomanometer (pressure cuff) in millimeters of mercury (mm Hg) and given as systolic over diastolic pressure. The upper number is the systolic pressure, which is the peak force of blood as the heart pumps it. The lower number is the diastolic pressure, which is the pressure when the heart is filling or relaxing before the next beat. Normal blood pressure for an adult is 120/70 (on average) Hypertension, or high

blood pressure, is defined as a reading of 140/90 on three consecutive measurements at least six hours apart. Hypertension is a major cause of stroke.

1.3. Types of Hypertension:

There are two major types of hypertension and four less frequently found types.

The two major types are:

1. Primary or essential hypertension
2. Secondary hypertension

The other types include:

- ❖ Malignant Hypertension.
- ❖ Isolated Systolic Hypertension
- ❖ White Coat Hypertension
- ❖ Resistant Hypertension

1.3.1. Primary or essential hypertension:

Primary hypertension has no specific origin but is strongly associated with lifestyle. It is responsible for 90 to 95 percent of diagnosed hypertension and is treated with stress management, changes in diet, increased physical activity and medication (if needed).

1.3.2. Secondary hypertension:

Secondary hypertension is responsible for 5 to 10 percent of diagnosed hypertension. It is caused by a preexisting medical condition such as congestive heart failure, kidney failure, liver failure, or damage to the endocrine (hormone) system.

1.4. Stages of Hypertension:

The concept of "stage of hypertension" was determined in the U.S. by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7).

There are three stages of hypertension:

1. Prehypertension
2. Stage 1 Hypertension
3. Stage 2 Hypertension

Categories for blood pressure levels in adults are given in Table no.1

TABLE: 1 CATEGORIES FOR BLOOD PRESSURE LEVELS IN ADULTS

	Blood Pressure Level (mmHg)		
Category	**Systolic**		**Diastolic**
Normal	< 120	and	< 80
Prehypertension	120-139	or	80-89
High Blood Pressure			
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥ 160	or	≥ 100

1.5. Treatment of hypertension[3]:

Medications that lower blood pressure are often referred to as antihypertensive drugs. Generally these drugs are classified by how they work.

- Diuretics
- Beta-adrenergic blocking agents
- Calcium channel blockers
- Angiotensin converting enzyme (ACE) inhibitors
- Angiotensin II Receptor Blockers (ARBs)
- Vasodilators

1.6. Angiotensin II Receptor Blockers (ARBs):

The renin-angiotensin system, specifically angiotensin II, is implicated in the pathogenesis of essential hypertension, renovascular hypertension, congestive heart failure, and renal diseases associated with albuminuria. Blockade of the rennin-angiotensin system with ACE inhibitors has provided effective treatment of these conditions; however, some of the adverse effects of ACE inhibitors appear to be unrelated to angiotensin II blockade. For example, cough and angioedema are due to other effects of ACE inhibition, such as degradation of bradykinins and prostaglandins.

ARBs are used for controlling high blood pressure, treating heart failure and preventing kidney failure in people with diabetes or high blood pressure. They may also prevent diabetes and reduce the risk of stroke in patients with high blood pressure and an enlarged heart. ARBs may also prevent the recurrence of atrial fibrillation.

1.6.1. ARBs have the following actions:

- Dilate arteries and veins and thereby reduce arterial pressure and preload and afterload on the heart.
- Down regulate sympathetic adrenergic activity by blocking the effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.
- Promote renal excretion of sodium and water (natriuretic and diuretic effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of aldosterone secretion.

- Inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure, and myocardial infarction.

1.7. General Introduction:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

1.8. Current technologies in oral drug delivery:

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations, such as Tablets, Capsules, Sachets, Suspensions, Emulsions, and Solutions, they are superior to the

conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral DDS may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

1.8.1. Immediate-Release Preparations:

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

1.8.2. Controlled-Release Preparations:

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within

the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

1.8.3.Targeted-Release Preparations:

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints. Some of the potential CR and site-specific DDSs will be described.

1. LITERATURE REVIEW:

Akira et al.,[1] reported that candesartan cilexetil,8 mg/day, significantly reduced the progression of CHF when compared with placebo. This 6-month study examined the safety and efficacy of candesartan cilexetil, 8 mg once daily, to prevent the progression of congestive heart failure (CHF).

Omari et al.,[2] reported that complex formation of candesartan with β- cyclodextrins prepared by freeze drying method is chemically not stable due to the formation of amorphous candesartan and compression enhances the instability of candesartan. In this study the DSC thermograms for CAND/β-CyD complexes proved the formation of inclusion complexes with new solid phase. MM studies indicate the partial penetration of CAND into the β-CyD cavity.

Franks et al.,[3] reported that candesartan cilexetil effectively reduced BP as demonstrated by CBPM and ABPM measurements and was well tolerated in this group of hypertensive children. In this study, eleven patients (mean age 14.2 y) received a final candesartan cilexetil median daily dose of 8 mg (0.13 mg/kg, range 2–16 mg). Study treatment resulted in significant reductions in systolic and diastolic BP as measured by CBPM (–7.4%, p = 0.03 and –5.9%, p = 0.01, respectively) and by ABPM (–6.0%, p = 0.03 and –10.8%, p = 0.006, respectively), but no significant reductions as measured by HBPM. No clinically significant changes in laboratory measures were observed and patients reported nonspecific mild adverse effects.

Erdmann et al.,[4] reported that candesartan cilexetil is safe when compared with placebo in the treatment of patients with CHF. This study involved a blinded, independent review of all adverse event data and was performed to assess all-cause mortality and unexpected deaths, and hospitalisations for acute deterioration of CHF, chronic progression of CHF, other intercurrent events, or accidental injury/attempted suicide. The descriptive analysis included crude and cumulative incidence rates for mortality and cardiac and non-cardiac morbidity using the Kaplan-Meier method and the log-rank test. The results demonstrated a clinically non-significant trend for all relevant events.

Graham et al.,[5] reported that candesartan cilexetil is an effective BP-lowering drug when used alone or in combination with amlodipine or amlodipine plus hydrochlorothiazide in the treatment of moderate-to-severe essential hypertension. This study evaluated the efficacy of candesartan cilexetil, an angiotensin II type 1 receptor antagonist, used alone or in combination with amlodipine or in combination with amlodipine and hydrochlorothiazide in the treatment of patients with moderate-to-severe essential hypertension. The result demonstrated that candesartan is an effective BP-lowering drug when used alone or in combination with amlodipine or amlodipine plus hydrochlorothiazide and was well tolerated throughout the investigation.

Toblli et al.,[6] reported that candesartan cilexetil provides a significant protective role against morphologic changes in vessels as well as in cavernous spaces of the erectile tissue, caused by high blood pressure, in SHR. This present study was performed to determine whether an angiotensin II receptor blocker could protect cavernous tissue (CT) from these structural alterations in SHR. Male SHR and Wistar-Kyoto (WKY) rats were studied during 4 months. Rats were divided into three groups: SHR (n=10), SHR with candesartan cilexetil (n=10) and WKY rats (n=10). Candesartan cilexetil 7.5 mg/kg/day was administered orally throughout the study. CT was processed for pathology studies. The amount of (1) cavernous smooth muscle (CSM), (2) vascular smooth muscle (VSM), (3) collagen type III, and the rat endothelial cell antibody (RECA-1)/tunica media ratio in cavernous arteries were evaluated.

Baguet et al.,[7] reported that candesartan significantly reduces the incidence of cardiovascular death, hospital admissions for decompensated heart failure, and all-cause mortality in chronic heart failure patients with altered left ventricular systolic function, when added to standard therapies or as an alternative to ACE inhibitors when these are poorly tolerated. Furthermore, the study showed that candesartan can protect against myocardial infarction, atrial fibrillation and diabetes. Tolerance to candesartan is good, but blood pressure and serum potassium and creatinine levels must be monitored.

Baguet et al.,[8] reported that candesartan and amlodipine besylate treatments may alter identically the natural progression of carotid IMT in hypertensive type 2 diabetic patients. This study consists of 36 months and investigated the effect of candesartan cilexetil (CC) on the common carotid intima-media thickness (IMT) vs amlodipine besylate (AML) in patients with

type 2 diabetes and mild to moderate essential hypertension. No significant differences were observed between the two groups for change in IMT at M12 (−0.001 vs −0.027 mm/year for CC and AML respectively, p = 0.425), at M24 (−0.033 vs −0.019 mm per year respectively, p = 0.442). The augmentation in carotid lumen diameter from baseline was statistically greater in the AML group at the last visit (p = 0.034). BP variations during the study were similar in the two groups.

Homma et al.,[9] reported that combination therapy with ARB plus ACEI/amlodipine proves beneficial than the ARB monotherapy in nondiabetic renal disease. Present study compared the effect of the combination therapy with ARB plus calcium antagonists/ACEI on proteinuria with that of the ARB monotherapy in chronic nondiabetic renal disease. At 1 month of the drug treatment, the candesartan monotherapy (n=19) reduced BP from 154±3/93±2 to 146±3/88± 2 mmHg (P<0.05), and a similar magnitude of BP reductions was observed with the combination therapy with candesartan plus ACEI/amlodipine (from 153±2/95±2 to 144±2/88± 2 mmHg, P<0.05, n=39). In contrast, the reduction in proteinuria was greater with the combination therapy (-52±3% at 12 months, n=39) than with the candesartan monotherapy (-25 ±3%, n=19) Since the reduction in BP was achieved to the same level, the distinct proteinuria-sparing action of these therapies is attributed to BP-independent mechanisms, which should vary depending on the agents used.

Pfister et al.,[10] reported that HD does not influence the elimination kinetics of candesartan. The observed inter- and intraindividual variability of oral clearance and the pronounced influence of HD-induced volume contraction on the haemodynamic effects of candesartan makes it mandatory to carefully monitor HD patients treated with candesartan cilexetil. It was a repeated dose study (8 mg candesartan cilexetil once daily) in eight male HD patients over a treatment period of 5 days with an additional observation period of 3 days. Pharmacokinetic analysis with nonlinear mixed effects modeling (NONMEM) over the whole treatment period revealed a dependency of the volume of distribution on body weight and of the metabolic clearance on age and body weight in the studied population. No significant drug elimination by HD was observed.

McClellan et al.,[11] reported that candesartan cilexetil is effective and well tolerated when used once daily (as monotherapy or in combination with other antihypertensive agents) in patients

with mild, moderate or severe hypertension. once daily, oral candesartan cilexetil 8 to 32mg dose-dependently and effectively reduces blood pressure in patients with mild to moderate essential hypertension. One study showed candesartan cilexetil 16 mg/day to be more effective than losartan potassium 50 mg/day. Furthermore, the combination of candesartan cilexetil with either hydrochlorothiazide or amlodipine resulted in additive antihypertensive effects. Pooled data indicate that the tolerability profile of the drug is not significantly different from that of placebo, with headache being the most commonly reported event. Adverse events are not dose related and are mostly mild to moderate in severity. Candesartan cilexetil is better tolerated than enalapril, primarily because of a reduced incidence of cough, and was not associated with the hypokalaemia or hyperuricaemia seen with hydrochlorothiazide in a study in patients aged ≥75 years.

See et al.,[12] reported that candesartan cilexetil is an effective antihypertensive agent that can be used alone or in combination with other antihypertensive drugs. It is generally well tolerated and may be an option for patients who cannot tolerate angiotensin-converting-enzyme inhibitors because of cough. In clinical trials, candesartan cilexetil has produced a dose-dependent effect when given in dosages of 2-32 mg/day. Observed trough-to-peak blood pressure ratios support a once-daily dosage regimen. The antihypertensive effect of candesartan cilexetil 4-16 mg/day was as great as that of enalapril 10-20 mg/day and amlodipine 5 mg/day and larger than that of losartan potassium 50 mg/day. Adding candesartan cilexetil to hydrochlorothiazide 12.5-25 mg/day and amlodipine 5 mg/day led to enhanced blood-pressure reductions and was well tolerated. It appears that candesartan can decrease renal perfusion without adversely affecting renal blood flow and may mediate a decrease in albuminuria in hypertensive patients with type 2 diabetes.

Stoukides et al.,[13] reported that Candesartan cilexetil provides an alternative antihypertensive therapy that is well tolerated and effective in reducing blood pressure in a wide range of patients. Due to its greater binding affinity to the angiotensin II receptor, candesartan cilexetil appears to have a longer antihypertensive effect than losartan. In this experiment the Study and review articles describing the chemistry, human pharmacology, pharmacodynamics, pharmacokinetics, placebo-controlled trials, comparative trials, and clinical application of candesartan cilexetil based on the published literature and premarketing clinical trials were

reviewed. The study showed that Candesartan cilexetil has demonstrated reductions in blood pressure comparable to those of enalapril, with the rate of adverse events greater in the enalapril group.

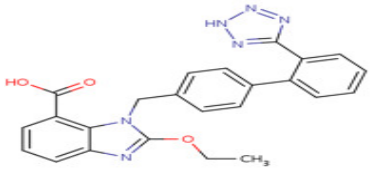
Vijaykumar et al.,[14] reported that the wet bead milling process coupled with spray granulation is a viable approach for developing nanoparticle formulations of biopharmaceutics classification system (BCS) class II compounds with enhanced solubility and faster dissolution. In this study the granules containing drug nanoparticles of KC, FF and CC were blended with extra-granular excipients using a double cone blender. The blend was subsequently compressed into tablets at the desired strength, and the physical properties of tablets — hardness, friability and disintegration time — were measured. Enhancing solubility and dissolution velocity of sparingly soluble compounds correlates with an improved pharmacokinetics profile and a concomitantly improved therapeutic outcome.

Fang Gao et al.,[15] reported that the nanoemulsion was very effective for enhancing the oral absorption of insoluble CC, and CCN showed the great potential for clinical application. In this work, a novel CC loaded nanoemulsion (CCN) was designed to improve the intestinal absorption. CCN was prepared by a modified emulsification-solvent evaporation technique. The physicochemical characteristics of CCN were characterized, and the intestinal absorption was investigated as well. The experimental results indicated that CCN was nanometer-sized droplets (35.5 ± 5.9 nm) with negative potential (– 6.45 ± 0.36 mV), and the absorption of CCN was significantly improved in total intestinal tract compared with free CC solution. The experimental results showed that the area under the concentration–time curve (AUC0–t) of candesartan was improved over 10-fold after CC was incorporated into CCN.

1.1. DRUG PROFILE:

Physiochemical nature of the Candesartan cilexetil is given in Table no. 2.

TABLE: 2 PHYSIOCHEMICAL NATURE OF CANDESARTAN

S.No	Physiochemical Nature	Description
1	Common Name	Candesartan cilexetil
2	Nature	Prodrug
3	State	Solid
4	Colour	White to off white
5	Taste	Sour to bitter
6	IUPAC Name	2-ethoxy-3-[[4-[2-(2H-tetrazol-5 yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid
7	Molecular Formula	$C_{24}H_{20}N_6O_3$
8	Chemical Structure	
9	Molecular Weight	**610.659660 [g/mol]**
10	Melting Point	**163^{0}C**
11	Solubility	**Sparingly soluble in methanol, insoluble in water**
12	Predicted Water Solubility	**7.71e-03 mg/Ml**

Pharmacological nature of Candesartan is given in table no.3

TABLE: 3 PHARMACOLOGICAL NATURE OF CANDESARTAN:

S.No	Pharmacological Nature	Description
1	Indication	For the treatment of hypertension and Heart Failure.
2	Mechanism of Action	Candesartan competes with angiotensin II for binding at the AT1 receptor subtype. As angiotensin II is a vasoconstrictor which also stimulates the synthesis and release of aldosterone, blockage of its effects results in a decrease in systemic vascular resistance.
3	Drug Interactions	Amiloride Increased risk of hyperkaliemia Drospirenone Increased risk of hyperkaliemia Lithium The ARB increases serum levels of lithium Potassium Increased risk of hyperkaliemia Spironolactone Increased risk of hyperkaliemia Triamterene Increased risk of hyperkaliemia
4	Phase 1 Metabolizing Enzymes	Cytochrome P450 11B2 (CYP11B2)
5	Targets	Type-1 angiotensin II receptor
6	BCS	Class II - Low Solubility and High Permeability

Pharmacokinetic nature of Candesartan is given in Table no.4

TABLE: 4 PHARMACOKINETIC NATURE OF CANDESARTAN:

S.No	Pharmacokinetic Nature	Description
1	Absorption	Bioavailability is about 15%
2	Distribution	Vd is 0.13 L/kg
3	Metabolism	Candesartan cilexetil is bioactivated by ester hydrolysis during absorption from the GI tract to candesartan. Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite.
4	Elimination	Primarily as unchanged drug in the urine and by the biliary route, in the feces. Plasma Cl is 0.37 mL/min/kg. Renal Cl is 0.19 mL/min/kg. About 26% is excreted unchanged in urine.
5	T_{max}	3 to 4 hrs
6	Half Life ($t_{½}$)	Approximately 9 hrs
7	Protein binding	More than 99%
8	Toxicity	No lethality was observed in acute toxicity studies in mice, rats and dogs given single oral doses of up to 2000 mg/kg of candesartan cilexetil

Product Specifications of Candesartan are given in Table no.5

TABLE: 5 PRODUCT SPECIFICATIONS OF CANDESARTAN

S.No	Product Specifications	Description
1	Drug Type	Approved
2	Dosage Form	Tablet
3	Route of Administration	Oral
4	Strength	4mg, 8mg, 16mg and 32mg
5	Non active Ingredients	Calcium CMC, maize starch, HPC, iron oxide lactose, magnesium stearate, PEG, Avicel.
6	Package	Blister Pack
7	Storage Conditions	Controlled room temperature
8	Available Brands	Amias, Atacand, Blopress, Ratacand

EXCIPIENT PROFILE:

MICROCRYSTALLINE CELLULOSE[44]:

Synonyms: Avicel, cellulose gel, crystalline cellulose, E460, Emocel, Fibrocel, Tabulose, Vivacel.

Functional Category: Tablet and Capsule diluent, suspending agent, adsorbent, tablet disintegrant.

Applications: As a diluent in tablets (wet granulation and direct compression) and capsule formulation. In addition to its use as a diluent, it also has some lubricant and disintegrant property.

Description: White-colored, odourless, tasteless crystalline powder composed of porous particles. Available in different particle size grades which have different properties and applications

Solubility: Slightly soluble in 5 % w/v NaOH solution, practically insoluble in water, dilute acids and most organic solvents.

Stability: It is a stable, though hygroscopic material.

Storage conditions: The bulk material should be stored in a well-closed container in a cool, dry, place.

Incompatibilities: Incompatible with strong oxidizing agents.

Safety: It is generally regarded as a nontoxic and nonirritant material.

Commercial Grades of Microcrystalline Cellulose

Grade	Nominal Mean Particle Size
Avicel PH 102 & 112	100 µm
Avicel PH 101 & 103	50 µm
Emocel 50 M	51 µm
Vivacel 102	100 µm
Vivacel 12	180 µm

LACTOSE[45]:

Synonyms: Fast-Flo, Microlose, milk sugar, Pharmatose, Tablettose.

Functional Category: Tablet and Capsule diluent.

Applications: As filler or diluent in tablets (wet granulation and direct compression) and capsules, in lyophilized products and infant fed formulas.

Description: White to off-white crystalline particles or powder, odourless and slightly sweet-tasting.

Solubility: Freely soluble in water, practically insoluble in chloroform, ethanol and ether.

Stability: Under humid conditions (80 % RH and above) mold growth may occur.

Storage conditions: Lactose should be stored in a well-closed container in a cool, dry, place.

Incompatibilities: A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown- colored

products.

Safety: Adverse reactions to lactose is largely attributed to lactose intolerance, which occurs in persons with a deficiency of the intestinal enzyme lactase

HYDROXY PROPYL CELLULOSE:

1. Nonproprietary Names

- BP: Hydroxypropylcellulose[31]
- JP: Hydroxypropylcellulose
- PhEur: Hydroxypropylcellulosum
- USPNF: Hydroxypropyl cellulose

2. Synonyms

Cellulose, hydroxypropyl ether; E463; hyprolose; Klucel; Methocel; Nisso HPC; oxypropylated cellulose.

3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Empirical Formula and Molecular Weight

The PhEur 2005 and USPNF 23 describe hydroxypropyl cellulose as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.6% of silica or another suitable anticaking agent. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50 000–1 250 000;

5. Structural Formula

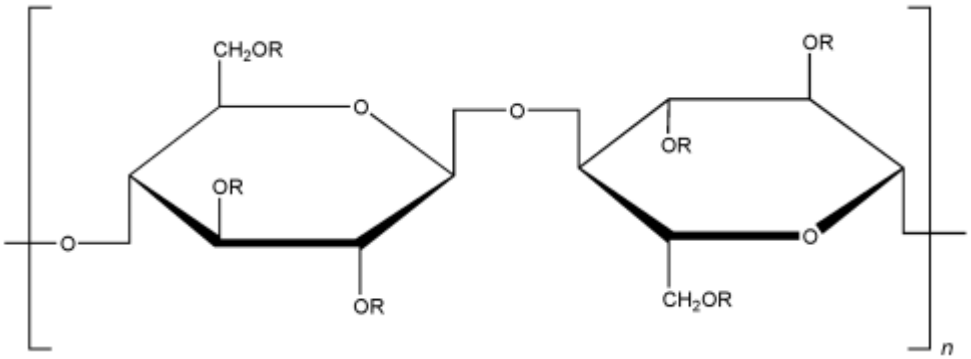


figure:8 : R is H or $[CH_2CH(CH_3)O]_mH$

6. Functional Category

Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations;

In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder,[1] film-coating,[2] and extended-release-matrix former.[3–5] Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes.[6–10] Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release.[11] The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. Typically, a 5% w/w solution of hydroxypropyl cellulose may be used to film-coat tablets. Aqueous solutions containing hydroxypropyl cellulose along with an amount of methyl cellulose or ethanolic solutions have been used.[12–14] Hydroxypropyl cellulose is also used in microencapsulation processes and as a thickening agent. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

8. Description

Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder.

Melting point:

Softens at 130°C; chars at 260–275°C.

MAGNESIUM STEARATE

1 Nonproprietary Names

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

2 Synonyms

Magnesium octadecanoate; octadecanoic acid, magnesium salt;
stearic acid, magnesium salt.

3Empirical Formula and Molecular Weight

C36H70MgO4 591.34

The USPNF 23 describes magnesium stearate as a compound
of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate (C32H62MgO4). The PhEur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids

.

4 Structural Formula

[CH3(CH2)16COO]2Mg

5 Functional Category

Tablet and capsule lubrica**nt.**

6 Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

7 Typical Properties

Crystalline forms: high-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk): 0.159 g/cm³

Density (tapped): 0.286 g/cm³

Density (true): 1.092 g/cm³

Flash point: 250ºC

Flowability: poorly flowing, cohesive powder.

Melting range:

117–150ºC (commercial samples);

126–130ºC (high purity magnesium stearate).

Solubility: practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%)

PG STARCH:

- Also called as starch derivative.
- Used as thickening agent,stabilizer or emulsifier.
- Soluble in cold water.
- Dryed by extrusion,drumdrying.
- Used to thicken instant desserts.

FERRIC OXIDE RED:

- Most common colorant in ceramics.
- It is very soft and fine powder.
- It is available from bright light red at a deep red marron.
- In oxidation firing ion is an important source for tan.

CALCIUM CMC:

- Molecular weight:201 m/w.
- It should be stable on storage.
- Grades like h,m,l are used.
- Used as emulsying agent,gelling agent,binding agent.

2. AIM & OBJECTIVES:

Aim of the study:

Candesartan cilexetil is an angiotensin II inhibitor (ARB) drug that is sold under the brand name "Atacand" in the United States by ASTRAZENECA. Patent expiration date for this product is on June 2012. So, the aim of the present study is to develop and evaluate Candesartan cilexetil (generic version) with respect to the reference sample for getting marketing approval in United States. The formulation of tablets were done to match the in-vitro drug release with respect to the reference drug and carry out the stability studies as per the ICH guidelines.

Objectives:

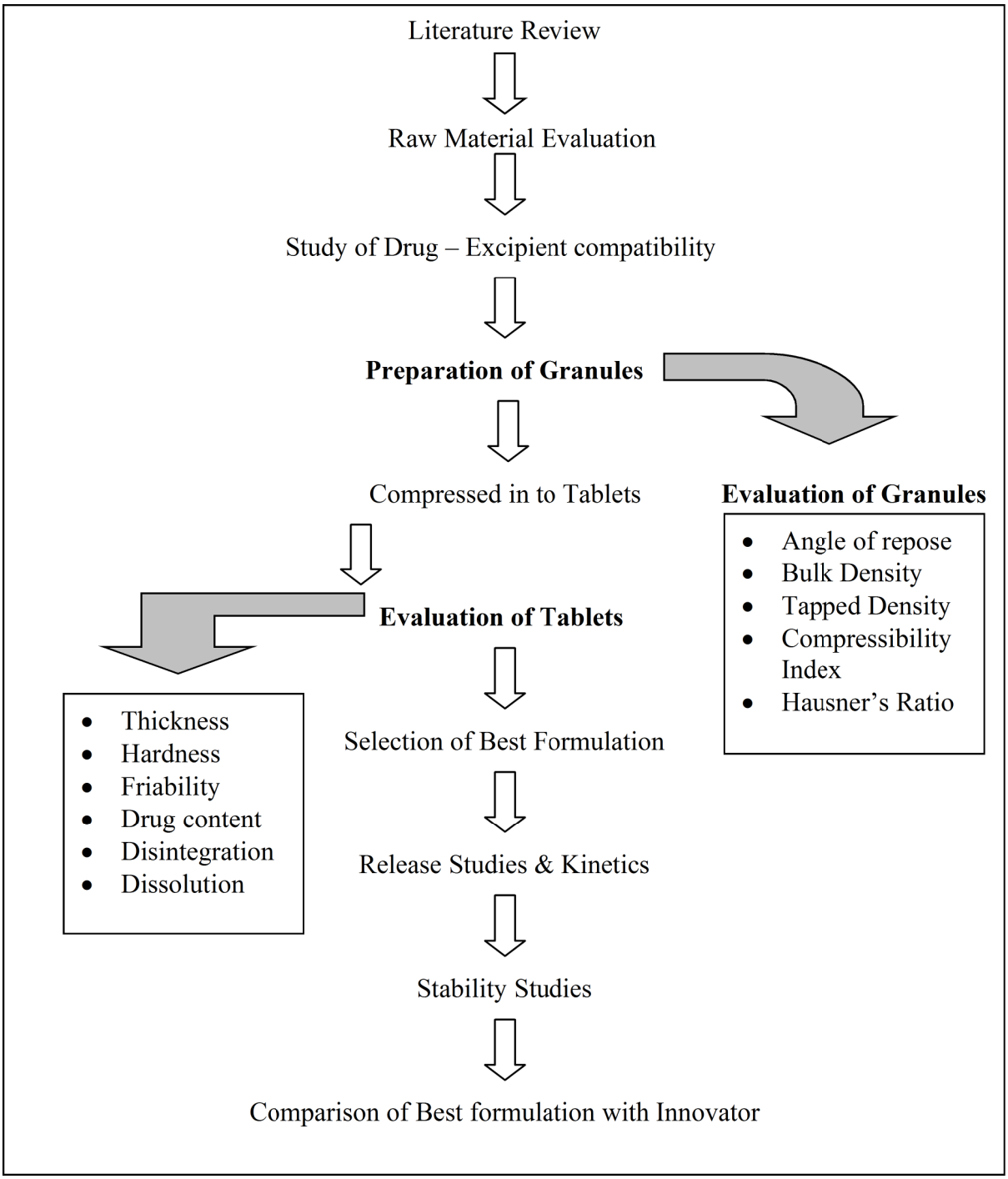
Primary Objective:

1. To formulate and evaluate immediate release candesartan cilexetil tablets (32mg)

Secondary Objectives:

1. To perform preformulation studies including drug – excipient compatibility study.
2. To develop various formulations with different excipients.
3. To study the effect of excipient concentrations on the tablet characteristics.
4. To establish the invitro release compliance with the established criteria.
5. To achieve immediate release profile for the developed formulation.
6. To establish the stability of the formulation.

3. PLAN OF WORK:



4. MATERIALS AND METHODS:

The list of materials used for the formulation of Candesartan immediate release tablets are given in Table no. 6.

TABLE: 6 LIST OF MATERIALS USED IN THE FORMULATION

S.No	Ingredients	Specification	Rationale	Source
1.	Candesartan Cilexetil	USP	API	Arabindo Pharmaceutical co.ltd
2.	Lactose Monohydrate	USP	Diluent	Avon organics Ltd
3.	PG Starch	USP	Filler/Binder	Arabindo Pharmaceutical Ltd
4.	Microcrystalline cellose (Avicel PH 101)	USP	Disintegrant	SD Fine Chemicals ltd
5.	Klucel – LF	USP	Binder	SD Fine Chemicals ltd
6	Ca. CMC	USP	Superdisintegrants	SD Fine Chemicals ltd
7	Mg. Stearate	USP	Glident	SD Fine Chemicals ltd
8	Purified water	USP	Solvent	NATCO Pharma Ltd

The list of equipments used for the formulation of Candesartan immediate release tablets are given in Table no.7.

TABLE: 7 LIST OF EQUIPMENTS USED FOR THE FORMULATION

Name of instrument	Model no.	Make
Electronic Weighing Balance	PR 203	Mettler Toledo
Tap Density Tester USP	ETD-1020	Electrolab
Electromagnetic Sieve Shaker	EMS-8	Electrolab
Electronic Moisture Analyzer	HG 63	Mettler Toledo
Tablet Compression Machine-8 station	MINI Press - II MT	Rimek
Digital Hardness Tester	TH 10503	Labindia
Disintegration Test Apparatus USP	ED-2AL	Electrolab
Friabilator USP	EF-2	Electrolab
Mechanical Stirrer	RQT-124D	Remi Motors
Pharma R&D Coater	Deluxe	Ideal Cures
Fluid Bed Drier	UT-150	Umang Pharmatech
Rapid mixture granulator	RMG 25	Anchormark
Multi Mill	MM 15	Anchormark
Weighing balance	T-26I	Scaletec Instruments (Citizen)
Tray Drier	PPT TD6	Platinum Pharmatech
Dissolution Test Apparatus Type II	UV-Pharmaspec – 1700	DBK Instruments Ltd., Mumbai.

5. METHODS:

4.1. PREFORMULATION STUDIES:

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients and their compatibility.

The API was tested for the following properties:

- Organoleptic Properties
- Solubility
- Water Content
- Particle Size determination
- Flow Properties
    - ❖ Angle of Repose
    - ❖ Bulk Density
    - ❖ Tapped Density
    - ❖ Carr's Index
    - ❖ Hausner's Ratio
- Drug – Excipient compatibility study

4.1.1. Organoleptic Properties:

The drug sample was viewed visually and viewed under the compound microscope for the determination of its color using the black and white backgrounds and nature of the drug sample. Then the results were compared with the official books and United States Pharmacopoeia.

4.1.2. Solubility:

The solubility of the drug sample was carried out in different solvents (aqueous and organic) according to the United States Pharmacopoeia. The results are then compared with those given in the official books and United States Pharmacopoeia.

4.1.3. Water Content:

Transfer 35 to 40ml of a mixture of methanol to the titration vessel and titrate with Karl fisher reagent to the electrometric end point to consume any moisture that may be present. Use powder from 5 tablets, grind to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results. Accurately weigh and transfer about 300-500mg of the powder in to the titration vessel, mix and titrate with the KF reagent to the electrometric endpoint. Calculate the water content of the specimen in mg taken by the formulae:

Calculation:

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where,

S = Volume in ml of reagent consumed in the second titration

F = Water equivalent factor of KF reagent

W = Weight of sample taken in mg

4.1.4. Flow Properties:

4.1.4.1. Angle of repose (θ):

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Procedure:

Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$$\text{Angle of Repose } (\Theta) = \text{Tan}^{-1} (H/R)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Acceptance criteria for Angle of Repose is given in the Table no.8.

TABLE: 8 ACCEPTANCE CRITERIA FOR ANGLE OF REPOSE

Range (^{0})	**Result**
31 – 35Excellent 25 – 30	Good
36 – 40	Fair
41 - 45	Passable
46 – 55	Poor
56 – 65	Very Poor
> 66	Very Very Poor

Acceptable range for angle of repose is 20^0 to 40^0.

4.1.4.2. Bulk density:

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder.

Procedure:

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 18 and 10 mg of pure drug was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula:

$$\mathbf{(Db) = M/Vo}$$

Where,

M = mass of powder taken

Vo= unsettled apparent volume

Limits:

It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

4.1.4.3 Tapped density:

Procedure:

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 10 mg of pure drug was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated.

Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (Vo). The tapped density (Dt) was calculated in g/ml by the formula:

$$Dt = M / Vo$$

Where,

M = weight of sample powder

Vo = final tapped volume

4.1.4.3. Compressibility Index and Hausner Ratio:

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such they are measures of relative importance of interparticulate interactions. In free flowing powder, such interactions are less significant and bulk & tapped density difference is close. For poorer flowing materials, this difference is greater.

a) Compressibility Index (% Compressibility):

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index was calculated using following equation:

$$\mathbf{CI\ (\%) = [(Dt - Db)/Dt] \times 100}$$

Where,

Dt = tapped density

Db = bulk density

b) Hausner's Ratio:

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula:

$$\mathbf{Hausner\ Ratio = Dt/Db}$$

Where,

Dt = tapped density

Db = bulk density

Acceptance criteria of flow properties are given in the Table no.9.

TABLE: 9 ACCEPTANCE CRITERIA OF FLOW PROPERTIES

Compressibility Index	Flow Character	Hausner Ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
> 38	Very Very Poor	> 1.60

4.1.5. Drug – Excipient Compatibility Study:

Drug is in intimate contact with one or more excipient in all the dosage forms. Later it could affect the stability of drug.Knowledge of drug excipient interaction is useful in selecting an appropriate excipient.

Procedure:

API and excipient are taken in the ratios above mentioned and mixed together in a polybag for 5 min. Each mixture is allotted sample code for identification. 4 sets of sample were allocated where each sample mixture is divided in to 1g in to its corresponding glass vial (USP Type I) at different conditions.

All vials are properly sealed and loaded at respective conditions. The samples are to be checked for its Description, Related substance and water content by KF.

Drug – Excipient ratio for compatibility study details are given in Table no.10.

TABLE: 10 DRUG – EXCIPIENT RATIO FOR COMPATIBILITY STUDIES:

S.No	Drug – Excipient	Ratio
1	Candesartan + Corn starc0h	1:5
2	Candesartan + PEG 6000	1:5
3	Candesartan + Calcium CMC	1:5
4	Candesartan + Klucel EF	1:5
5	Candesartan + Klucel LF	1:5
6	Candesartan + Ferric oxide red	1:0.1
7	Candesartan + Magnesium stearate	1:1
8	Candesartan + Avicel	1:5
9	Candesartan + Lactose	1:5

4.1.5.1. Sampling schedule:

The prepared drug and excipient mixtures were evaluated at various intervals for related substances by HPLC as per the following conditions and time intervals.Sampling schedule for compatibility study is given in Table no.11.

TABLE: 11 SAMPLING SCHEDULE:

S.No	Condition	Duration	No. of Sets
1	Initial	0 days	1
2	$55^0C \pm 2^0C$	14 days	1
3	40 ± 2^0C & 75 ± 5% RH	14 days	1
4	40 ± 2^0C & 75 ± 5% RH	28 days	1

4.1.5.2. Tests to be performed:

S.No	Parameters	Conditions			
		Initial	$55^0C \pm 2^0C$	40 ± 2^0C & 75 ± 5% RH	
		0 Day	14th Day	14th Day	28th Day
1	Physical Appearance	✓	✓	✓	✓
2	Related Substance	✓	✓	✓	✓

4.2. FORMULATION OF CANDESARTAN IR (32MG) TABLETS:

4.2.1. Formulation Planning:

The immediate release tablets containing 32mg Candesartan Cilexetil were prepared with a total tablet weight of 260mg. Based on the results of preformulation studies; to improve the flow properties tablets were prepared by Wet Granulation Technique and the composition are given in Table 1. Based on Literature survey and Compatibility Tests excipients like Microcrystalline Cellulose (pH 101), PEG – 6000, PGS, Hydroxypropyl cellulose, Carboxy Methyl Cellulose, Magnesium stearate were used.

4.2.2. Manufacturing Procedure:

- Weighed candesartan, Lactose and PG starch was passed through 40 mesh and then mixed.
- Weighed PEG 6000 is transferred into 50ml of purified water and then stirred by using mechanical stirrer to get clear solution.
- Weighed klucel poured in to above PEG solution and then stirred to get turbid solution by using mechanical stirrer.
- Above blend is made into dough mass by using this binder solution.
- This dough mass is passed through 14 mesh to get wet granules.
- These are dried by using FBD at 60^{o}c.
- Dried granules were passed through 18 mesh.
- Weighed Cal.CMC passed through 40 mesh and then added to above granules and then mixed.
- Weighed Mg.Stearate is passed through 40 mesh and then added to above blend and then mixed.
- Then compressed and punched.

4.3. EVALUATION OF FORMULATION:

4.3.1. Evaluation of granules:

4.3.1.1. Flow Properties:

The flow properties of the granules were evaluated as per the method described in the section 4.1.4.

4.3.1.2. Micromeretic properties:

The bulk density and tapped density of the granules were evaluated as per the method described in the section 4.1.4.3.

4.3.2. Evaluation of tablets:

4.3.2.1. Weight variation:

Weight variation was calculated as per method descried in USP. Twenty tablets were selected at random and their average weight was determined using an electronic balance. The tablets were weighed individually and compared with average weight.The requirements are met if the weights of not more than 2 of tablets differ by more than the percentage listed in the Table 12 and no tablets differ in weight by more than double that percentage.

Table: 12 Acceptance Criteria for Weight variation of Tablets

Average weight of tablet (mg)	Percentage difference allowed
≤130	10
130-324	7.5
>324	5

4.3.2.2. Tablet thickness:

Thickness and diameter of formulation trials were measured using a Digital Hardness Tester. Ten tablets of each trial formulation were taken and measured individually at frequent intervals.

4.3.2.3. Hardness:

Ten tablets from each batch were selected and hardness was measured using Digital hardness tester to find the average tablet hardness or crushing strength.

4.3.2.4. Friability (%):

Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in friabilator after the given specification (4 min at 25 rpm). The tablets were weighed again and % friability was then calculated by:

$$\%F = \{(W - W_0)/W\} \times 100$$

Where,

% F	=	Friability of tablets in percent.
W	=	Initial Wight of tablets.
W_O	=	Final weight of tablets.

4.3.2.5. Disintegration Test:

Disintegration test, measured using USP tablet disintegration test apparatus (ED2L, Electrolab, India) using 900 ml of distilled water at room temperature (37±20C).

4.3.2.6. In-vitro Dissolution Release study:

4.3.2.6.1. Dissolution conditions:

Medium	:	0.7% tween-20 in 0.05 M phosphate buffer, PH 6.5
Volume	:	900ml
Temperature	:	37°C ± 0.5°C
Apparatus	:	USP type –II (paddle)
RPM	:	50
Time interval	:	10, 20, 30, 45 and 60 min

4.3.2.6.2. Chromatographic conditions:

Column	:	Hypersill BDS-C8 (150 X 4.6mm) 5µm
Flow rate	:	1.5ml/min
Wave length	:	UV-210nm
Injection volume	:	10µL
Column temperature	:	40 °C
Run time	:	10min

4.3.2.6.3. Buffer Preparation:

Mix 1ml of orthophophoric acid in 1000ml of purified water. Filter the solution through 0.45µ membrane. Filter and degas.

4.3.2.6.4. Mobile phase preparation:

Prepare a filtered and degas mixture of buffer and acetonitrile in the ratio of 40:60 v/v respectively.

4.3.2.6.5. Standard preparation:

Accurately weigh and transfer about 35.5mg of candesartan cilexetil working standard in to a 200ml volumetric flask. Add about 20ml of acetonitrile, sonicate to dissolve. Cool the solution to room temperature and dilute to volume with dissolution medium. Transfer 5ml of standard stock preparation into a 25ml volumetric flask and dilute to volume with dissolution medium (0.05 M phosphate buffer, pH 6.5 containing 0.7% tween-20).

4.3.2.6.6. Sample preparation:

Place one tablet in each of six dissolution flasks containing 900ml of dissolution medium previously maintained at 37°C ± 0.5°C taking care to exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus specified time intervals.

After completion of each specified time interval withdraw a portion of solution from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1cm from vessel wall ad filter through 0.45µ membrane filter.

4.3.2.6.7. Procedure:

Separately inject equal volume (10 µL) of dissolution medium as blank, standard and sample preparations in to the chromatograph and record the chromatograms and measure the peak area responses for the analyte peak and calculate the % drug dissolved of candesartan in the portion of candesartan tablets taken by the formula:

4.3.2.6.8. Calculation:

% of labeled amount of candesartan dissolved:

$$\frac{TA}{SA} \times \frac{SW}{200} \times \frac{5}{25} \times \frac{900}{1} \times \frac{P}{100} \times \frac{100}{32}$$

Where,

SA = Peak area response due of candesartan from standard preparation

TA = Peak area response due of candesartan from sample preparation

SW = Weight of candesartan working standard (mg)

P = Purity of candesartan working standard

4.3.2.7. Assay (HPLC):

4.3.2.7.1. Chromatographic conditions:

Column	:	Hypersill BDS-C8 (150 X 4.6mm) 5µm
Flow rate	:	1.5ml/min
Wave length	:	UV-210nm
Injection volume	:	10µL
Column temperature	:	40 °C
Run time	:	25min

4.3.2.7.2. Preparations:

- **Mobile Phase – A:**

Mix 1ml of orthophophoric acid in 1000ml of purified water. Filter the solution through 0.45µ membrane. Filter and degas.

- **Mobile Phase – B:**

Acetonitrile – HPLC grade, Filter the solution through 0.45µ membrane filter.

- **Diluent Preparation:**

Prepare a degassed mixture of mobile phase A and acetonitrile in the ratio of 30:70 v/v respectively.

- **Standard preparation:**

Accurately weigh and transfer about 32mg of candesartan working standard in to 100ml volumetric, add 60ml of diluent and sonicate to dissolve. Cool the solution to room temperature and dilute to volume with diluent. Transfer 5ml of the above solution in to a 50ml volumetric flask and dilute to volume with diluent.

- **Sample preparation:**

Accurately weigh and transfer 5 tablets in to a 100ml volumetric flask. Add about 60ml of diluent and sonicate for 30min with occasional shakings. Cool the solution to room temperature and dilute to volume with diluent and mix. Filter the solution through 0.45µ membrane filter.

Transfer 2ml of the above filtered solution in to a 100ml volumetric flask and dilute to volume with diluent.

4.3.2.7.3. Procedure:

Separately inject equal volume of diluent as blank, standard and sample preparations in to the chromatograph and record the chromatograms and measure the peak area responses for the analyte peak and calculate the % content of candesartan in the portion of candesartan tablet taken by formula:

4.3.2.7.4. Calculation:

% of content of candesartan cilexetil:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{5}{50} \times \frac{100}{TW} \times \frac{100}{2} \times \frac{P}{100} \times \frac{Avg\ Wt}{LA} \times 100$$

Where,

SA	=	Peak area response due of candesartan from standard preparation
TA	=	Peak area response due of candesartan from sample preparation
SW	=	Weight of candesartan working standard (mg)
P	=	Purity of candesartan working standard
TW	=	Weight of sample
LA	=	Label amount

5. RESULTS AND DISCUSSIONS:

5.1. Preformulation studies:

Preformulation studies like Physical Characterization, Solubility, Moisture Content, Flow properties like Angle of Repose, Bulk Density, Tapped Density, Compressibility Index, Hausner ratio and Compatibility studies were performed and the obtained data are presented in the Table no.13,14,15.

5.1.1. Physical Characterization of API:

TABLE: 13 RESULTS OF PHYSICAL CHARACTERIZATION OF THE DRUG

S.No:	Description	Result
1.	Appearance	White to off-white powder
2.	Odour	Characteristic odour.
3.	Solubility	Freely soluble in Methylene chloride. Slightly soluble in methanol, Practically insoluble in water.
4.	Water Content	0.07 %

The above result shows that physical characterization of the drug candidate (API) complies with the USP specifications.

5.1.2. Flow Properties:

TABLE: 14 RESULTS OF FLOW PROPERTIES

S.No	Flow Properties	Result
1	Bulk density (g/ml)	0.581
2	Tapped density (g/ml)	0.714
3	Carr's index (%)	18.62
4	Hausner's ratio	1.22
5	Angle of repose	$22^{o}.8^{l}$

From the above results, it is found that the API has **"fair"** flow properties.

5.1.3. Compatibility studies results:

TABLE: 15 COMPATIBILITY STUDIES RESULTS

Excipients	% known impurities			% Unknown impurities			Total impurities		
	I	II	III	I	II	III	I	II	III
Lactose	0.15	0.2	0.3	0.01	0.02	0.04	0.4	0.6	0.8
PEG 6000	0.1	0.15	0.4	0.04	0.05	0.08	0.2	0.4	0.7
PG Starch	0.1	0.12	0.3	0.02	0.05	0.09	0.1	0.3	0.5
HPC	0.2	0.25	0.35	0.02	0.04	0.08	0.2	0.3	0.6
Ca CMC	0.2	0.18	0.28	0.01	0.04	0.05	0.3	0.5	0.9
Mg.Stearate	0.1	0.15	0.18	0.03	0.04	0.05	0.2	0.3	0.5

I = INITIAL
II = LONG TERM (28 DAYS)
III = ACCELERATED (14 DAYS)

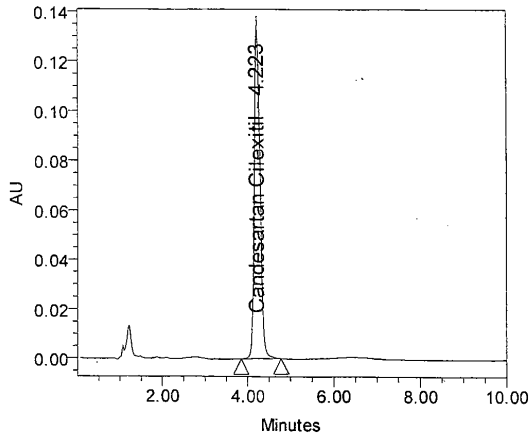
No Characteristic change in the color of the powder and no additional degradation of the product was observed. The increase in impurities at the end of the accelerated condition is not significant. All the excipients are stable and compatible with active ingredient. Hence, it is recommended that the above excipients can be used in further formulation development trials.

Analytical Evaluation:

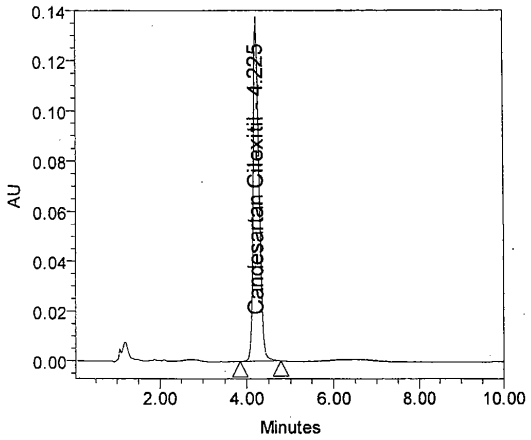
Standard Chromatograms:

Blank Chromatogram:

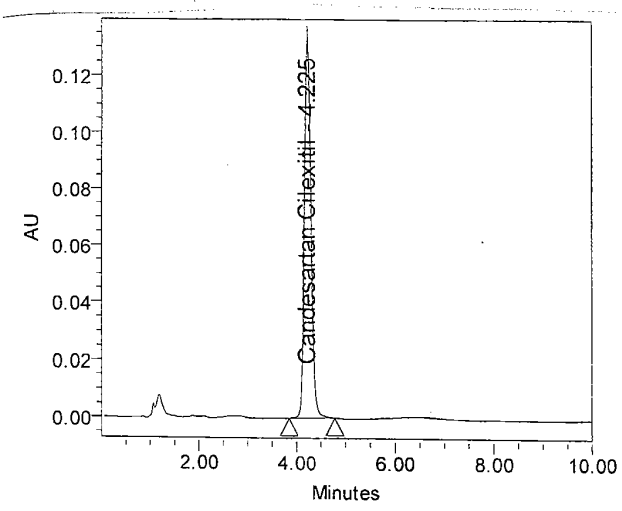
Reported by User: RD Development (Developme Project Name: CANDESARTAN CILEXETIL TABLETS



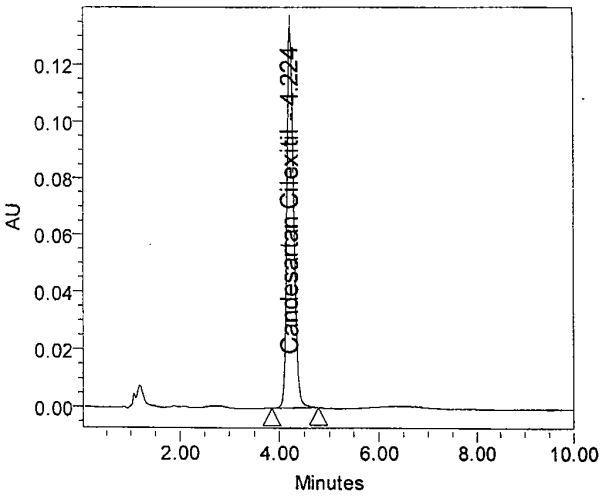
Sample Name Candeesartan Disso Std SST; Vial 2; Injection 1; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm



Sample Name Candeesartan Disso Std SST; Vial 2; Injection 2; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

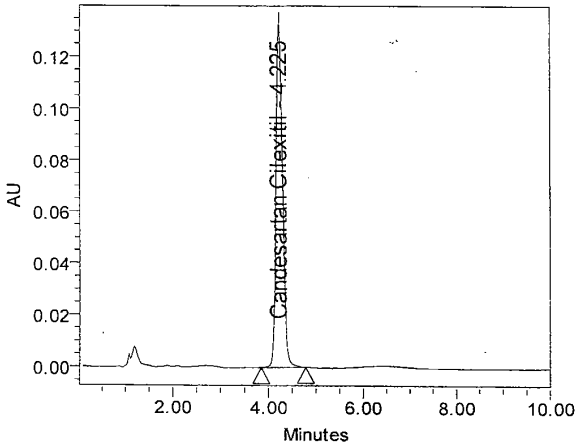


Sample Name Candeesartan Disso Std SST; Vial 2; Injection 3; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

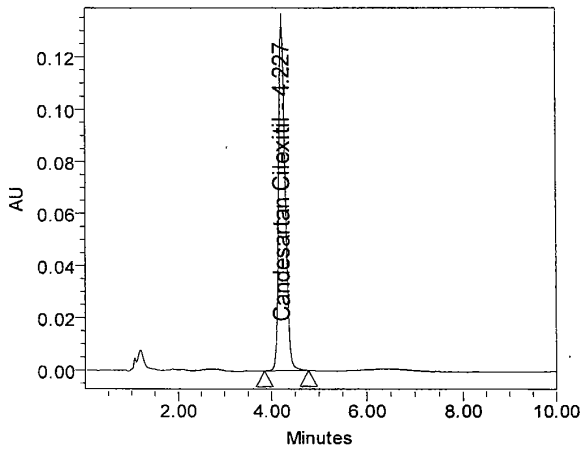


Sample Name Candeesartan Disso Std SST; Vial 2; Injection 4; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

Reported by User: RD Development (Developme Project Name: CANDESARTAN CILEXETIL TABLETS



Sample Name Candeesartan Disso Std SST; Vial 2; Injection 5; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm



Sample Name Candeesartan Disso Std SST; Vial 2; Injection 6; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

Component Summary Table
Name: Candesartan Cilexitil

	SampleName	Name	RT	Area	USP Tailing	USP Plate Count
1	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1280775	1.2	4566.1
2	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281249	1.2	4545.8
3	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281033	1.2	4521.9
4	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281567	1.2	4515.7
5	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1280872	1.2	4504.2
6	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1279184	1.2	4467.7
Mean			4.2	1280780	1.15	4520.2
Std. Dev.				831.71		
% RSD				0.06		

FORMULATION TRIALS:

The Immediate Release tablets of Candesartan 32mg has been formulated as described in the section 4.2 and the formula is shown in the table 16

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10**
Candesartan	32	32	32	32	32	32	32	32	32	32
Lactose Mono Hydrate	155.98	155.98	164.97	164.97	166.97	162.5	162.5	52	-	164.97
PEG 6000	12	12	6	2	-	6	6	12	-	6
Lycatab PGS/ Corn starch	40	40	40	40	40	40	40	25	25	40
Ferric oxide Red	0.02	0.02	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Klucel LF	8	8	8	12	12	10	10	12	12	8
Avicel	-	-	-	-	-	-	-	100	150	-
Purified Water	70	70	70	70	70	60	70	70	120	70
Ca CMC	11.2	11.2	8	2	8	8	8	25	25	8
Mg.stearate	0.8	0.8	1.0	1	1	1.5	1.5	2	2	1.0
Total (mg)	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**	**260**

F – 1 & 2: Formulate candesartan cilexetil (32mg) by using unmicronized and micronized API**.**

Objective: These Trials are done to determine whether particle size vary with dissolution rate and flow properties or not

Inference: Micronized API (F – 2) showed good flow properties with required Dissolution**.**

F – 3: Formulate candesartan cilexetil by reducing PEG and ca CMC concentration.

Objective: These Trials are done to match the Innovator in terms of Appearance, Thickness, Hardness and to achieve 80% drug release within 10 min.

Inference: Did not achieve required Hardness and Drug release

F – 4: Formulate candesartan cilexetil by reducing PEG and Increasing Klucel.

Inference: Did not achieve required drug content.

F – 5: Formulate candesartan cilexetil without PEG.

Inference:

a) Achieved required Hardness
b) Did not achieve required Drug release

F – 6 & 7: Formulate candesartan cilexetil by changing the water quantity

Objective: These Trials are done to determine the effect of the water quantity

Inference:

a) F – 6 (60ml): Decrease in Hardness
b) F – 7 (70ml): Increase in Hardness

F – 8: Formulate candesartan cilexetil by incorporating Avicel PH 101 and reducing Lactose, Starch.

Objective: These Trials are done to determine the effect of Avicel PH 101 on the hardness and drug release

Inference: Achieved required Drug release

F – 9: Formulate candesartan cilexetil by incorporating Avicel PH 101 and eliminating Lactose, PEG.

Inference: Achieved required Hardness and Drug release

F – 10: Formulate candesartan cilexetil using Direct Compression.

Objective: The objective of this trial is to formulate candesartan cilexetil using direct compression technique

Inference: Resulted in Poor Flow properties.

From the above trials F -8 is considered the best formulation

RESULTS OF FLOW PROPERTIES OF LUBRICATED BLEND:

The evaluation results for flow properties of granules are described in the following table 17.

Table No: 17 **Evaluation of Granules:**

S.No	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
1	F-1	0.596	0.785	24.07	1.31
2	F-2	0.581	0.714	18.60	1.22
3	F-3	0.654	0.802	18.45	1.22
4	F-4	0.694	0.834	16.67	1.2
5	F-5	0.480	0.625	23.07	1.30
6	F-6	0.694	0.833	16.66	1.2
7	F-7	0.625	0.781	20.00	1.25
8	F-8	0.609	0.781	21.95	1.28
9	F-9	0.510	0.641	20.40	1.25
10	F-10	0.500	0.735	32	1.470

Inference:

A. F – 1, F – 5, F – 8 showed "Passable" flow properties
B. F-2, F-3, F-4, F-6, F-7, F-9 showed "Fair" flow properties
C. F – 10 showed very poor flow properties

RESULTS OF EVALUATION OF TABLETS:

The evaluation results of in process properties of tablets are described in the following table 18.

Table No: 18 Evaluation of Tablets:

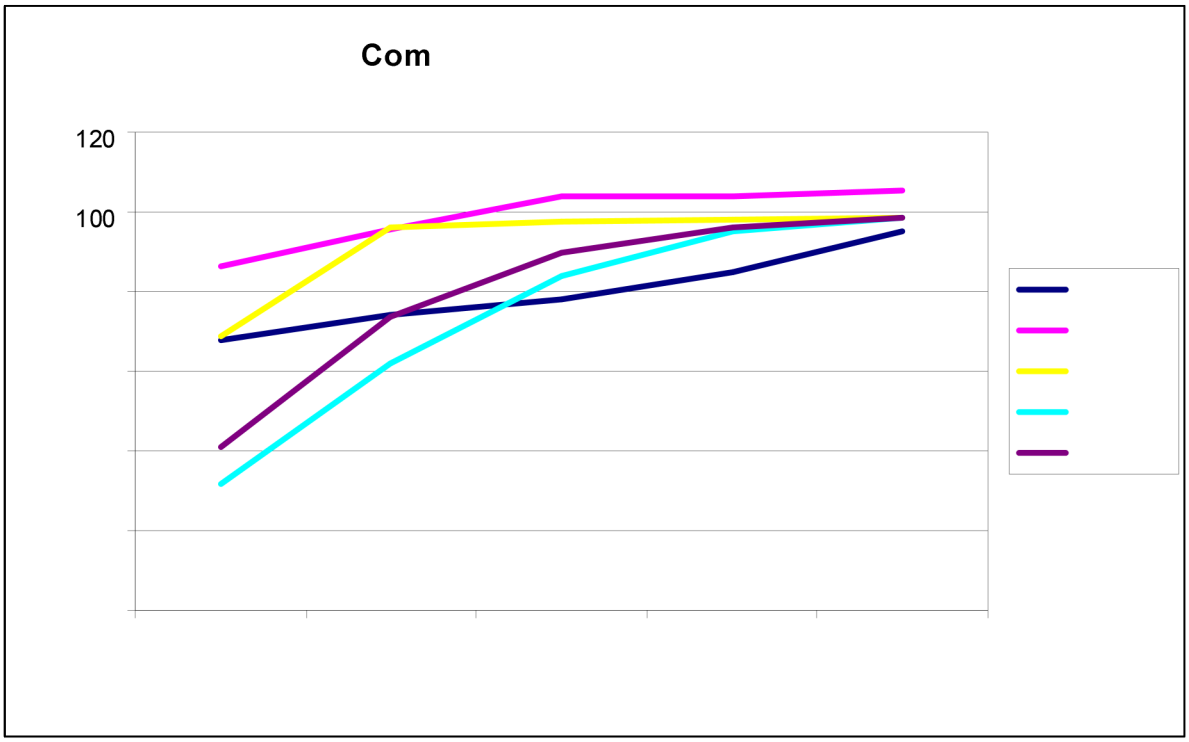
S.No	Formulations	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (%)
1	F-1	3.62 ± 0.0097	4.1 ± 0.031	3.16	0.153
2	F-2	3.62 ± 0.0166	5.1 ± 0.032	3.02	0.106
3	F-3	3.46 ± 0.0353	6.19 ± 0.22	8.5	0.377
4	F-4	3.46 ± 0.0244	9.75 ± 0.514	14.55	0.24
5	F-5	3.48 ± 0.0294	10.44 ± 0.492	11.5	0.17
6	F-6	3.47 ± 0.0531	7.1 ± 0.278	12	0.28
7	F-7	3.47 ± 0.0526	9.45 ± 0.59	12	0.23
8	F-8	3.53 ± 0.0222	8.12 ± 0.472	11	0.06
9	F-9	3.55 ± 0.0194	9.6 ± 0.354	5.5	0.06
10	F-10	3.55 ± 0.0163	7.1 ± 0.278	2	0.167
11	Innovator	3.50 ± 0.049	9.8 ± 0.14	11.17	0.15

IN-VITRO DISSOLUTION RELEASE:

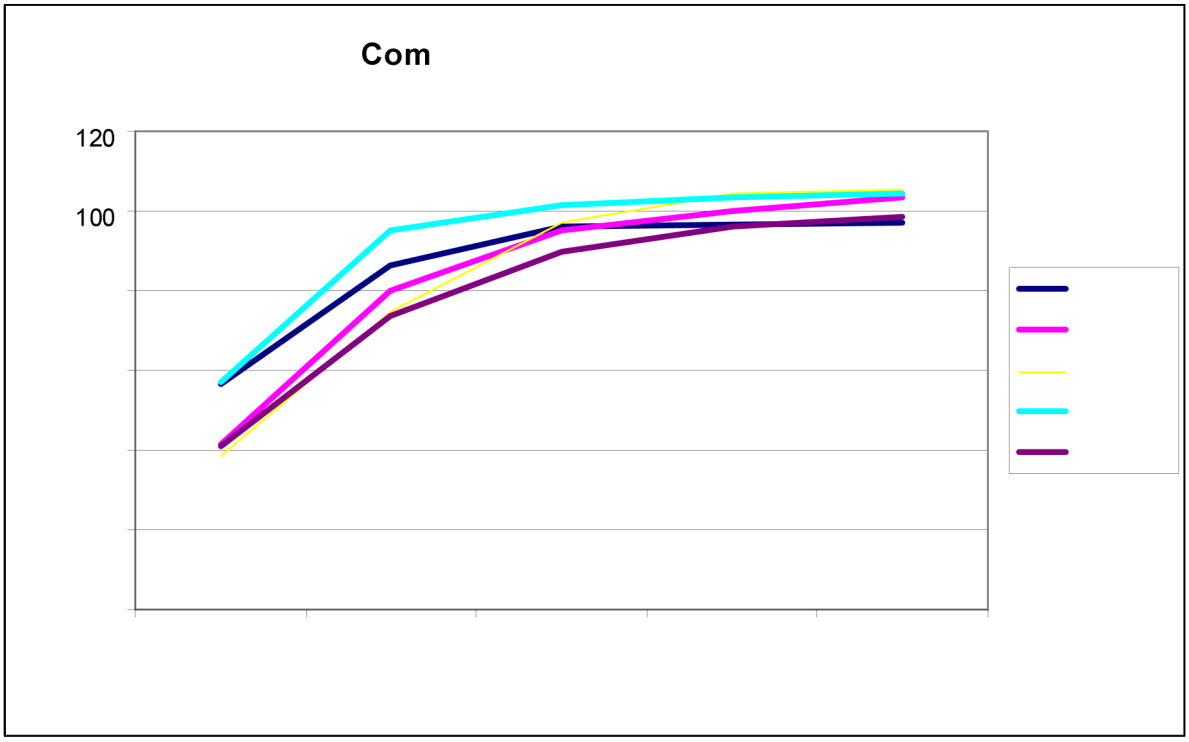
Comparative In-vitro Dissolution release profile for Reference and all formulations at 60 Minutes is given in the table 19

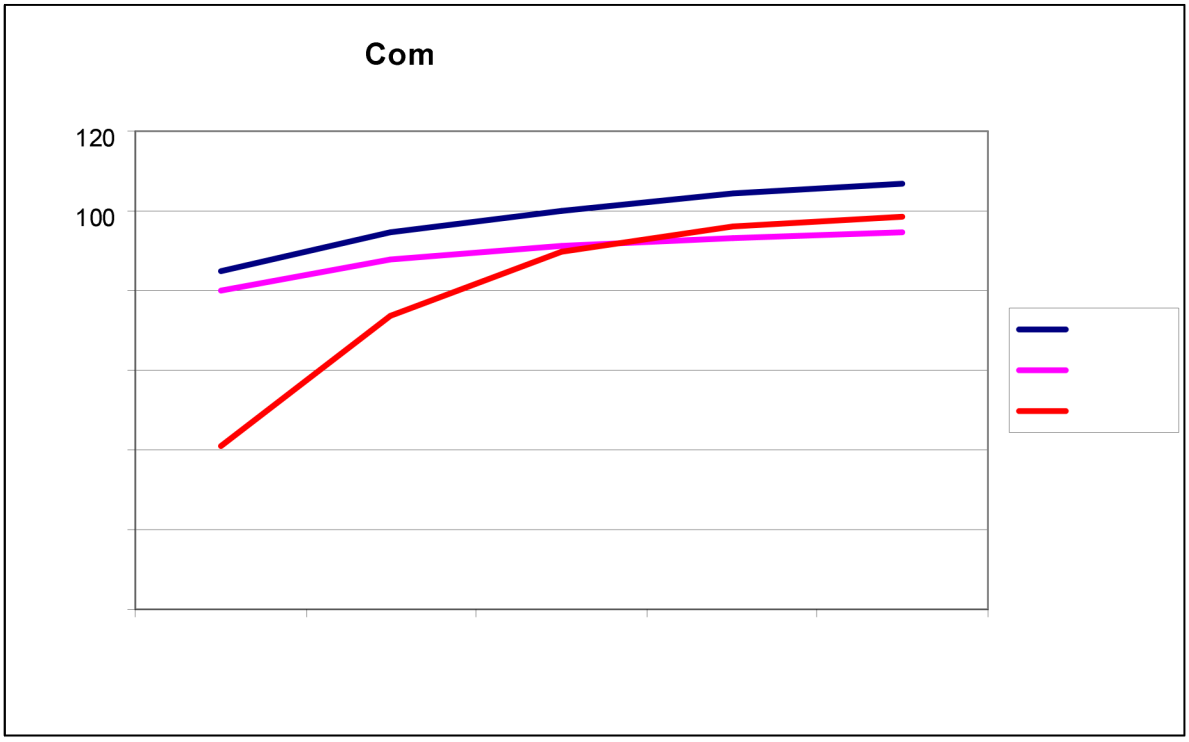
Table No: 19 % of Drug Release (Candesartan Cilexetil):

S.No	Time	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	Innovator
1	10	67.6	86.4	68.9	31.6	56.5	41.4	38.4	56.9	84.7	80	40.9
2	20	72.4	95.8	96	61.8	86.5	79.9	74.5	95	94.7	87.8	73.7
3	30	77.9	103.8	97.6	84.0	96.2	94.9	97.0	101.3	99.9	91.2	89.6
4	45	84.6	104.5	97.9	94.9	96.4	100.1	104.3	103.6	104.6	93.4	96.2
5	60	92.5	106.5	98.6	98.3	97.1	102.6	106.5	104.4	107.0	94.7	98.6


Com
120
100

.


Com
120
100



Based on these parameters we have optimized F – 08 as the best formulation and decided as the final formula.

Stability Data of Trial F – 08:

Dissolution of trial F – 08 tablets were comparable with reference product. So tablets of this batch were kept for stability studies.

After 3 months the physical parameters of the tablets were same. Water content and related substance are with in limits. Tablets were passing the stability studies. The tablets were tested for average weight, thickness, hardness, friability, Disintegration, water content and RS at initial, 1 month and 3 months.

Table No:20 Stability Study data of Trial F – 08:

S.No	Parameters	Conditions			
		Initial	**$25^0C \pm 2^0C$**	**40 ± 2^0C & 75 ± 5% RH**	
		0 Day	**3 Months**	**1 Month**	**3 Month**
1	Average Weight	260.2 ± 0.13	260.2 ± 0.13	260.2 ± 0.13	260.2 ± 0.13
2	Thickness	3.53 ± 0.02	3.51 ± 0.04	3.52 ± 0.06	3.48 ± 0.02
3	Hardness	8.12 ± 0.47	7.8 ± 0.24	8.1 ± 0.36	7.7 ± 0.45
4	Friability	0.06	0.3	0.17	0.21
5	Disintegration	11	10	11	9
6	Assay	99.8	101.9	97.7	94.3
7	Water Content (%)	4.6	3.8	4.2	4.5

SUMMARY

The study was undertaken with an aim to formulate and evaluate conventional candesartan cilexetil(32mg) (generic version) with respect to the reference sample for getting marketing approval in United States.

API characterization was performed in aspects of colour, form ,taste, melting point, solubility .Preformulation studies were carried and the results were found to be satisfactory. Experimental started with the Process variables such as Bulk density, Tapped density,Angle of repose,Compressibility index of API.Drug excepient compatibility test were performed and the compatible excepients were selected for Formulation development.

Conventional tablets of candesartan cilexetil were prepared by wet granulation technique. The formulated tablets were evaluated for Drug content,Hardness, Friability,Disintegration time, Dissolution rate characteristics.The results were compared with Innovator product.

CONCLUSION

•Candesartan cilexetil is white to off white crystalline powder,Bitter to taste

• Candesartan cilexetil is freely soluble in solvents like Methylene chloride,6.5 Ph buffer , slightly soluble in Methanol, practically insoluble in Water.

•The compatibility study results Explain that there is no characteristic change in the colour of the powder and no additional degradation of the product was observed. The increase in impurities at the end of the Accelerated condition is not significant.All the excepients are stable and compatible with active ingredient.Hence,it is recommended that the above Excepients can be used in further formulation development trials.

• Conventional tablets of candesartan celexitil were prepared by Wet granulation Technique. All the tablets prepared fulfilled the Official USP Requirements of Drug content , Hardness, Friability and Disintegration time.

•The Dissolution of the drug followed 1 order kinetics in all formulations.

•F1 and F2 showed good flow properties with required Dissolution.

•F3 did not achieve required hardness and drug release.

•F4 did not achieve required drug content.

•F5 has adequate hardness and doesn't achieve Drug release.

•F6 and F7 decrease in hardness and increase in hardness.

•F9and F10 resulted in poor flow properties.

•F8 showed higher dissolution when compared to the other formulations and Innovator product.

Hence the increase in Dissolution of F8 may be due to the presence of PEG-6000, LACTOSE MONOHYDRATE AND AVICEL pH 102.

Stability studies were performed for this batch for 1 and 3 months under Accelerated and long term conditions.Finally after the duration, the product was analyzed for physical appearance, Hardness,Thickness, Friability,Loss on drying, disintegration, Assay and Related substance. The results obtained were found to be with in the specified limits.

The bigger scale confirmatory batch is under 6 months Accelerated stability condition, based on the result, a pilot scale will be executed.

After passing the above tests, the in-vivo studies (BA/BE Studies) will be executed to correlated the bioequivalence of best formulation (**Trial F – 08)** with the reference drug.

BIBLIOGRAPHY:

1. Akira Matsumori. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. Eur J Heart Fail (2003) 5 (5): 669-677.

2. Alaa A. Al Omaria, Mahmoud M. Al Omarib, Adnan A. Badwanb, Khaldoun A. Al-Sou'oda. Effect of cyclodextrins on the solubility and stability of candesartan cilexetil in solution and solid state. Journal of Pharmaceutical and Biomedical Analysis (2010) 3, 124-135.

3. Amy M Franks, Catherine E O'Brien, Cindy D Stowe, Thomas G Wells MD. Candesartan Cilexetil effectively reduces blood pressure in hypertensive children. The Annals of Pharmacotherapy 2008 July: Vol. 42, No. 10, 1388-1395.

4. Erland Erdmann, Michael George, Bernhard Voet, Doris Kolb. The safety and tolerability of candesartan cilexetil in CHF. Journal of Renin-Angiotensin-Aldosterone System March 2000. Vol. 1, No. 1, Suppl 31-36.

5. Graham A. MacGregor; J. Reuven Viskoper, Tarek F.T. Antonios, Feng J. He. Efficacy of Candesartan cilexetil alone or in combination with amlodipine and hydrochlorothiazide in moderate-to-severe hypertension. Hypertension 2000, 36:454.

6. Toblli J E , Stella I , Mazza O N , Ferder L, Inserra F . Candesartan cilexetil protects cavernous tissue in spontaneously hypertensive rats. International Journal of Impotence Research (2004) 16, 305–312.

7. Jean-Philippe Baguet, Gilles Barone-Rochette, Yannick Neuder. Candesartan cilexetil in the treatment of chronic heart failure**.** Volume 2009:5 Pages 257 – 264.

8. Baguet JP, Asmar R, Valensi P, Nisse-Durgeat S, Mallion JM. Effects of candesartan cilexetil on carotid remodeling in hypertensive diabetic patients: the MITEC study. Vol no. 2009:5 Pages 175 – 183.

9. Homma K , Hayashi K , Kanda T , Yoshioka K , Takamatsu I , Tatematsu S , Kumagai H , Wakino S, Saruta T . Beneficial action of candesartan cilexetil plus amlodipine or

ACE inhibitors in chronic nondiabetic renal disease. Journal of Human Hypertension (2004) 18, 879–884.

10. Marc Pfister, Franziska Schaedeli, Felix J Frey, Dominik E Uehlinger. Pharmacokinetics and haemodynamics of candesartan cilexetil in hypertensive patients on regular haemodialysis. Br J Clin Pharmacol.1999 June, 47(6): 645–651.

11. McClellan K.J, Goa K.L. Candesartan cilexetil: a review of its use in essential hypertension. Volume 56, November 1998 (5) 847-869(23)

12. See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. American Journal of Health-System Pharmacy, Vol 57, Issue 8, 739-746.

13. Stoukides CA, McVoy HJ, Kaul AF. Candesartan cilexetil: an angiotensin II receptor blocker. Ann Pharmacother. 1999, Dec 33(12):1287-98.

14. Vijaykumar Nekkanti, Pradeep Karatgi, Mahendra Joshi, Raviraj Pillai. Developing nanoparticle formulations of poorly soluble drugs. Pharmaceutical technology europe, nov 1, 2008.

15. Fang Gao, Zhiwen Zhang, Huihui Bu, Yan Huang, Zhiwei Gao, Jianan Shen, Chunjie Zhao, Yaping Li. Nanoemulsion improves the oral absorption of candesartan cilexetil in rats: Performance and mechanism. Journal of Controlled Release 2010 (2) 347-369(23).